



# **Armed Forces College of Medicine AFCM**



# **Lecture Title**

## **Glycogen storage diseases**

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## INTENDED LEARNING OBJECTIVES (ILO)

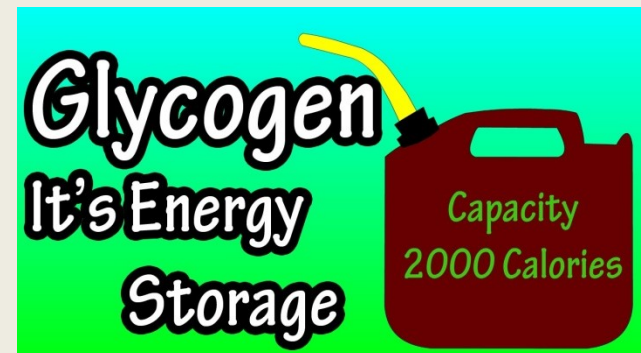


**By the end of this lecture the student will be able to:**

- 1- Explain the regulation of glycogenesis and glycogenolysis
- 2- Interpret biochemical basis of glycogen storage diseases



## Regulation of Glycogen Metabolism



# Regulation of Glycogen metabolism

- The principal enzymes controlling glycogen metabolism are :

(glycogen synthase & phosphorylase.)

- Glycogen synthase and phosphorylase are **reciprocally** regulated.

# 1. Allosteric Control

## \* Glycogen synthase:

- Stimulated by **G-6-P & ATP**
- Inhibited by **glycogen (product)**

## \* Glycogen Phosphorylase

- Stimulated by **AMP (muscle)**.
- Inhibited by **glucose and ATP**.

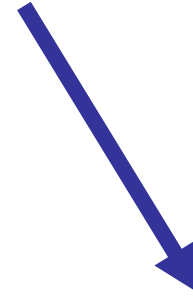
## **2. Covalent Modification**

# Glycogen synthase



**Activated by  
dephosphorylat  
ion**

**Glycogen  
synthase**



**Inactivated  
by  
phosphorylat**

**Glycogen  
synthase**

**P**

# Glycogen phosphorylase



**Activated by  
phosphorylation**

**Glycogen  
phosphoryla  
se**

**P**



**Inactivated by  
dephosphorylation**

**Glycogen  
phosphoryla  
se**

**Adrenaline and glucagon**

**Insulin**

**Adenyl cyclase**

**phosphodiesterase**

ATP → cAMP → AMP

active protein kinase

phosphorylation

**Glycogen synthase**

**Glycogen phosphorylase**

**Active**

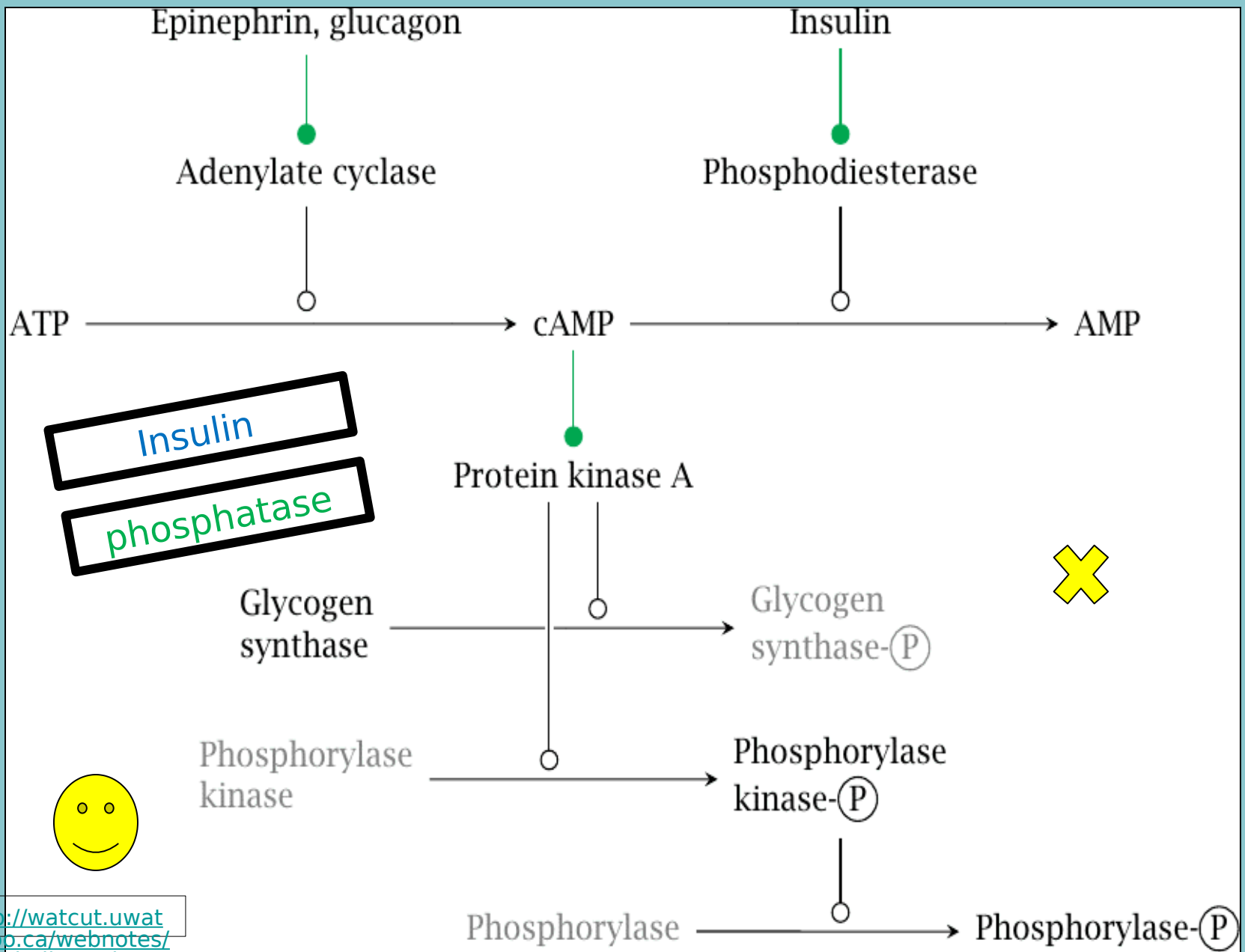
**Inactive**  
**Glycogenesis**

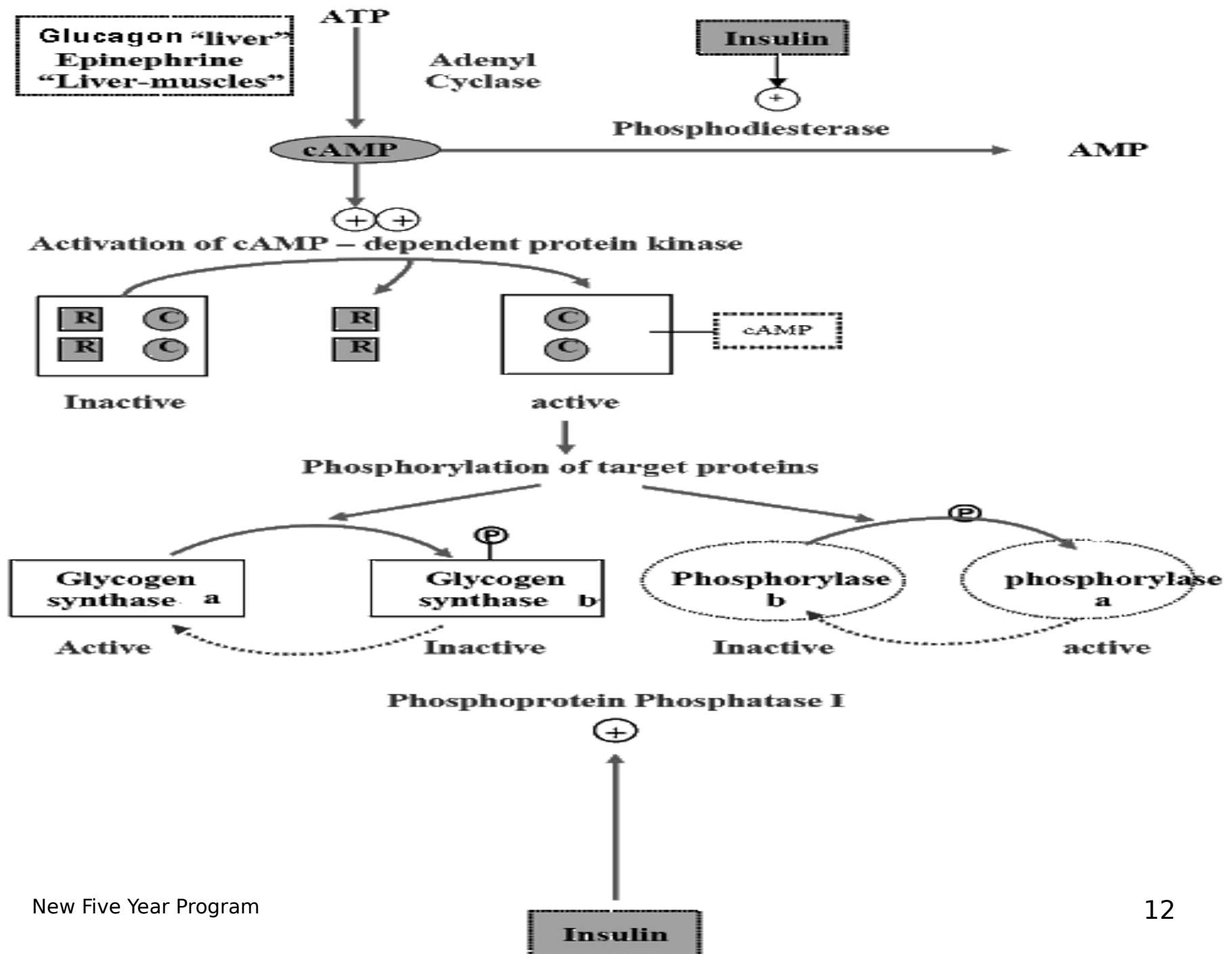
**Glycogenolysis**

Musculoskeletal & integumentary module

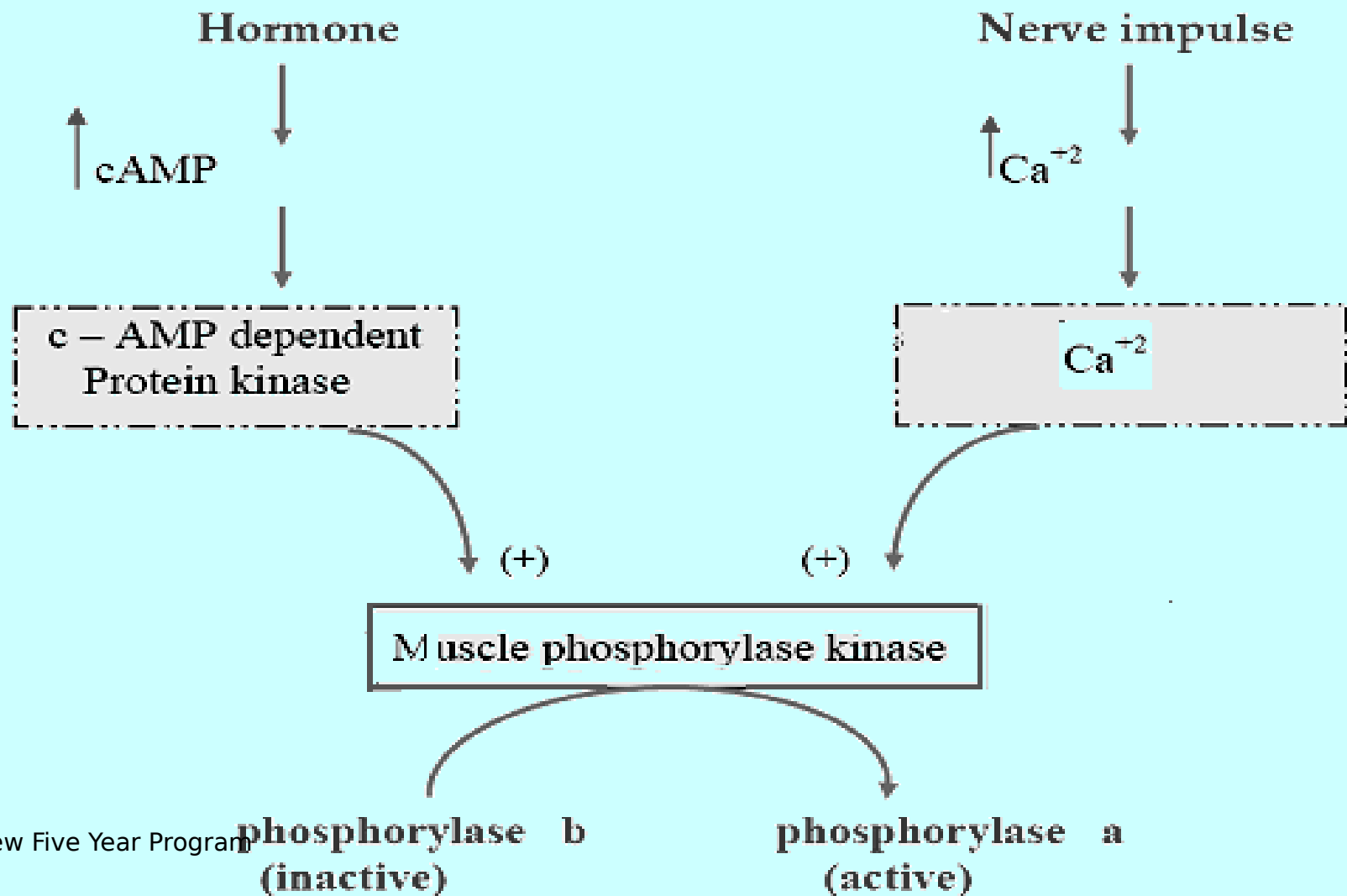
Program







# Activation of Glycogen phosphorylase kinase



# Quiz



**Describe regulatory  
effect of insulin on  
glycogen metabolism**

# Case



- A 12 years old boy presented to the pediatrician by his mother. He had a history of repeated episodes of **weakness, sweating** and pallor relieved by eating. His development was delay.
- On physical examination, the doctor found an enlarged firm liver, the liver biopsy revealed **high glycogen content**

# Laboratory results

**Fasting Blood glucose level:** 45 mg/dl (N:70-100mg/dl)

**Lactate:** 24mg/dl (N: up to 16mg/dl)

**Triglycerides:** 313 mg/dL (N:<150mg/dl)

**Cholesterol:** 302 mg/dl (N:<200 mg/dl)

**Uric acid:** 7.2 mg/dl (N: up to

# Glycogen storage diseases



## Definition:

Glycogen storage diseases are group of inherited disorders characterized by accumulation of large amount or abnormal type of glycogen in the cell.

# Glycogen storage diseases

**Table 21.1** Glycogen-storage diseases

Type	Defective enzyme	Organ affected	Glycogen in the affected organ	Clinical features
<b>I</b> <b>Von Gierke</b>	Glucose 6-phosphatase or transport system	Liver and kidney	Increased amount; normal structure.	Massive enlargement of the liver. Failure to thrive. Severe hypoglycemia, ketosis, hyperuricemia, hyperlipemia.
<b>II</b> <b>Pompe</b>	$\alpha$ -1,4-Glucosidase (lysosomal)	All organs	Massive increase in amount; normal structure.	Cardiorespiratory failure causes death, usually before age 2.
<b>III</b> <b>Cori</b>	Amylo-1,6-glucosidase (debranching enzyme)	Muscle and liver	Increased amount; short outer branches.	Like type I, but milder course.
<b>IV</b> <b>Andersen</b>	Branching enzyme ( $\alpha$ -1,4 $\rightarrow$ $\alpha$ -1,6)	Liver and spleen	Normal amount; very long outer branches.	Progressive cirrhosis of the liver. Liver failure causes death, usually before age 2.
<b>V</b> <b>McArdle</b>	Phosphorylase	Muscle	Moderately increased amount; normal structure.	Limited ability to perform strenuous exercise because of painful muscle cramps. Otherwise patient is normal and well developed.
<b>VI</b> <b>Hers</b>	Phosphorylase	Liver	Increased amount.	Like type I, but milder course.
<b>VII</b> <b>Tarui's Disease</b>	Phosphofructokinase	Muscle	Increased amount; normal structure.	Like type V.
<b>VIII</b>	Phosphorylase kinase	Liver	Increased amount; normal structure.	Mild liver enlargement. Mild hypoglycemia.

## Glycogen storage diseases (cont.)

Disease	Defective enzyme	Glycogen structure	Clinical manifestations
Type IX	phosphorylase kinase	Normal	Calf hypertrophy, mild generalized weakness, regression in motor development
Type X	phosphoglycerate mutase	Normal	Late onset myopathy, muscle cramps
Type XII	Aldolase A	Normal	Hypoglycemia

# Von Gierke's Disease ( Type I ) :

- It is the most common type
- Deficiency of **glucose - 6 - phosphatase** of the liver.
- **What about muscle**

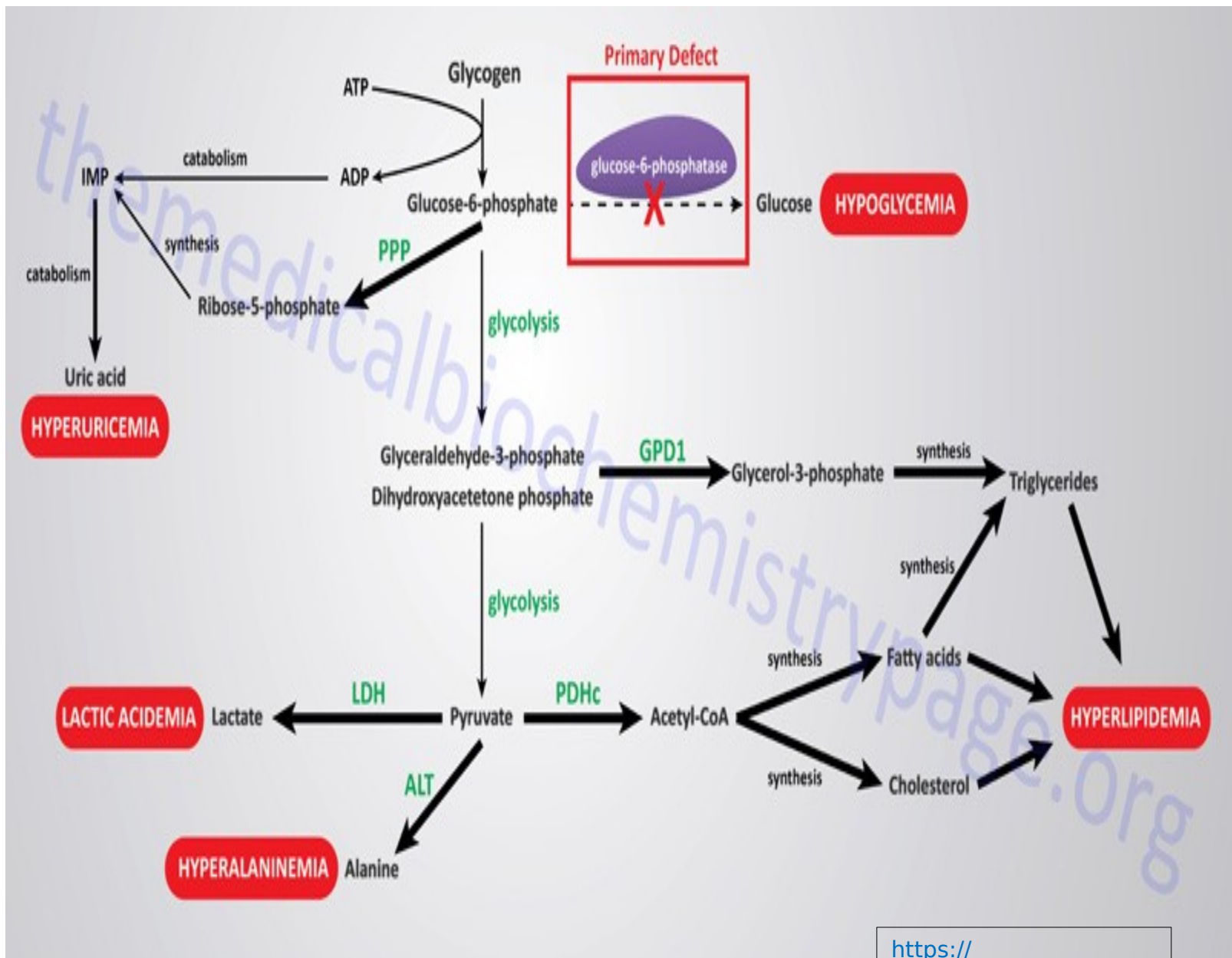


# The characteristic feature is

1. Fasting hypoglycemia & lactic acidosis
2. Hepatomegaly
3. Hyperlipidemia & ketosis .
4. Hyperuricemia & arthritis .

**\*Children fail to grow and die**





# Mc Ardle's Disease (Type V)

- Deficiency of muscle Glycogen phosphorylase
- Results in accumulation of muscle glycogen & decreased energy for muscle contraction, lead to:

1. Painful muscle cramps during exercise.
2. Release of some muscle enzymes such as CK & LDH and increased

<b>Glycogenolysis</b>	<b>Glycogenesis</b>	
<b>Breakdown of glycogen in liver and muscle</b>	<b>Synthesis of glycogen in liver and muscle</b>	<b>Definition</b>
<b>Cytoplasm</b>		<b>Site</b>
<b>Glycogen phosphorylase Debranching enzyme</b>	<b>Glycogen synthase Branching enzyme</b>	<b>Key enzymes</b>
<b>Glycogen</b>	<b>Glucose-6p UDP-glucose Glycogenin</b>	<b>Substrate</b>
<b>Glucose-6 phosphate in muscle Glucose in liver</b>	<b>Glycogen</b>	<b>Product</b>

<b>glycogenolysis</b>	<b>Glycogenesis</b>	
<b>Fasting state</b>	<b>Well fed state</b>	<b>Condition</b>
<ul style="list-style-type: none"> <li>- Stimulated by <b>AMP (muscle)</b>.</li> <li>- Inhibited by <b>glucose and ATP</b>.</li> </ul>	Stimulated by - <b>G-6-P &amp; ATP</b> Inhibited by - <b>glycogen (product)</b>	<b>Allosteric regulation</b>
<b>Activated by- anti-insulin hormones (glucagon, epinephrine)</b>  <b>Activated by- phosphorylation</b>  <ul style="list-style-type: none"> <li>- Inactive <b>phosphatase and phosphodiesterase</b></li> </ul>	<b>Activated by - insulin</b>  <ul style="list-style-type: none"> <li>- Activated by <b>dephosphorylation (through phosphatase and phosphodiesterase)</b></li> <li>- Inactive by</li> </ul>	<b>Covalent modification</b>

# **Important points**

- **The regulation of glycogenesis and glycogenolysis**
- **Glycogen storage diseases**

# Lecture Quiz



**Which of the following is important for glycogenesis?**

1. Glycogen phosphorylase
2. cAMP
3. Glucagons
- ④ 4. glycogenin
5. Glycogen phosphorylase kinase



**Von Gierk's disease is due to deficiency of:**

- 1. Glycogen phosphorylase enzyme in liver**
- 2. Glycogen phosphorylase enzyme in muscles**
- 3. Glucose-6- phosphatase enzyme in muscles**
- ④ Glucose-6- phosphatase enzyme in liver**

## SUGGESTED TEXTBOOKS



- **References:**
- Lippincott's Illustrated Reviews- 6<sup>th</sup> edition.
- Harper's Illustrated Biochemistry-29<sup>th</sup> edition.

